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COMBINED EFFECTS OF IONIZING RADIATION AND
ANTICHOLINESTERASE EXPOSURE ON RODENT MOTOR PERFORMANCE
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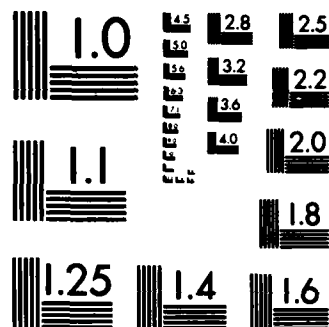
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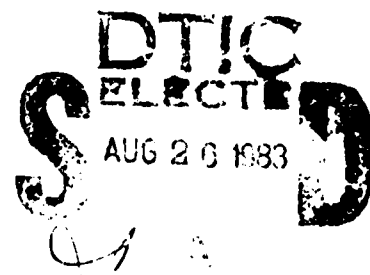
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COMBINED EFFECTS OF IONIZING RADIATION AND ANTICHOLINESTERASE EXPOSURE ON RODENT MOTOR PERFORMANCE

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USAF SCHOOL OF AEROSPACE MEDICINE
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NOTICES


This final report was submitted by personnel of the Vulnerability Assessment Branch, Radiation Sciences Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 7757-05-58.

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.


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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) Ionizing radiation and anticholinesterase exposure produce a performance decrement. The objective of this study was to determine if combined exposure would produce a greater deficit than either insult present alone. Five behavioral measures were taken on four experimental test groups. The test groups consisted of: (1) sham controls, (2) radiation exposure only (7 Gy), (3) physostigmine exposure only (0.1 mg/kg), and (4) radiation-plus physostigmine exposure.		

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20. ABSTRACT (Continued)

The behavioral measures were: (1) ability to maintain balance on a rotating rod, and (2) four measures of general motor activity in an activity monitor--crossings, rearings, groomings, and boli excreted. Animals were evaluated on the behavioral test battery three times postirradiation (45 min, 4 days, and 8 days).

The radiation-only test group had a 30% performance deficit at 45 min post-irradiation which decreased to a 60% deficit by Day 8. The physostigmine test group had a 40% deficit for each of the test periods. The combined treatment group showed a 60% performance deficit on each of the test periods. All measures of performance indicated that the combined exposure to ionizing radiation and physostigmine was much greater than either insult alone. The extent of the performance deficit was task dependent and appears to be a nonlinear function. The underlying mechanisms are not yet known.

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COMBINED EFFECTS OF IONIZING RADIATION AND ANTICHOLINESTERASE EXPOSURE ON RODENT MOTOR PERFORMANCE

INTRODUCTION

Ionizing radiation exposure results in a performance deficit as does exposure to chemical defense agents. The objective of this research was to determine the behavioral effect of combined treatment of ionizing radiation and an anticholinesterase. Three lines of research suggest that combined exposures may be more detrimental than either insult presented alone: (A) radiation exposure produces differential performance deficits as a function of time postexposure; (B) a reduced blood cholinesterase level produces a performance deficit; (C) ionizing radiation and chemical defense agents produce a decrease in blood cholinesterase activity. These lines of research are considered next.

A. Postradiation Performance: Motor ability after x-ray exposure (3-10 Gy at 0.25 Gy/min; 1 Gy = 100 rad) has been described in rats via a swimming time task (9). Increased performance (sustained swimming) was noted during the first week postexposure. By the second week postexposure, swimming ability was greatly reduced. The magnitude of depression was dependent upon the size of the x-ray dose. Irradiated animals surviving the period of testing recovered sufficiently by the ninth week postirradiation to attain their preirradiation performance level. Numerous other studies have also evaluated performance as a function of time postirradiation (3, 4, 6, 7, 10). The common finding was a change in performance as a function of time postirradiation.

B. Agent Exposure and Performance: An anticholinesterase such as physostigmine reduces cholinesterase activity and produces performance decrements in overt behavior, conditioned reflexes, learning, and motivation (2, 8). Motor ability has been tested in mice on a rotarod task where they were required to maintain their balance on a 3.2-cm diameter rod which was turning at 16.5 rpm (11). An 80% performance decrement was reached between 10 and 15 min postinjection (0.2 mg/kg, subcutaneously). Similar performance decrements have been reported in rats employing a pole jumping task (12). In this case, physostigmine produced a maximum effect at 0.25 mg/kg between 30 and 50 min postinjection.

C. Blood-Cholinesterase Activity: Rats, mice, guinea pigs, dogs, and rhesus monkeys have been tested for cholinesterase activity following radiation exposure (14). In most cases a decrease in cholinesterase has been observed. The decrease in cholinesterase activity was maximum 45 min postirradiation (10 Gy, x-rays). Williams (15) exposed male rats to gamma radiation from a ^{60}Co source and found that whole blood cholinesterase activity was depressed approximately 17%, particularly in the 3 to 10 days postradiation period. The degree of decreased activity was dose dependent up to the highest level tested (6 Gy). Similar findings are also reported by Tominz (13). A 0.2 mg/kg dose of physostigmine has also been shown to reduce mouse blood cholinesterase by 30% (5).

The combined data on anticholinesterase and radiation-induced cholinesterase reductions suggest that the combined effects of radiation and anticholinesterase exposures would prove more detrimental than either insult presented alone. Consideration of the above data led to the test parameters used in this study. The effects of physostigmine exposure (0.1 mg/kg) were evaluated preexposure and at three postirradiation times: 4 days, 8 days, and the point at which blood cholinesterase activity was most affected by irradiation (45 min). A radiation dose which produces large differences in performance across time was selected: 7 Gy (9).

METHODS

Experimental Design

Performance measures were taken on two behavioral tasks at one pre-irradiation and three postirradiation times. Eighty-six trained animals (Sprague Dawley male rats, 300 ± 25 g) were randomly assigned to the test groups listed in Table 1 (Test times 1-4 respectively). Each group was tested 24-hr preirradiation, and 45 min, 4 days, and 8 days postirradiation. Repeated testing and anticholinesterase injections of the groups required the use of an anticholinesterase which was rapidly metabolized. Physostigmine was the anticholinesterase of choice. The effects of physostigmine exposure are pronounced within the first 2 hours postinjection with a return to normal, thereafter. Although groups 2 and 4 received a physostigmine injection at each postirradiation test period, the previous exposure was not expected to affect the results; i.e., the effects due to a second injection are not influenced by the residual effects from a previous exposure (11).

TABLE 1. EXPERIMENTAL CONDITIONS AND TEST GROUPS

		Radiation level	
		Sham	7 Gy ^b
Physostigmine (mg/kg)	Placebo	1 ^a	3
	0.1	2	4

^aGroup number (N = 20 for group 2; N = 22 for others).

^bAt 0.7 Gy/min, ⁶⁰Co Source.

Behavioral Tests

The test battery for each testing period consisted of: monitoring general behavioral activity and evaluating motor coordination as measured by the rat's ability to remain on a moving rod (rotarod). General behavioral activity was monitored while the animal was in a 3 X 3 X 1 ft container. The floor of the container was marked off in 1 ft² segments. Each animal was placed in the middle square at the start of the 2.5-min recording period. The following activities were monitored: (1) crossings--each time the animal transversed one of the floor markings, (2) rearings--each time the animal

lifted both front paws from the floor without subsequent grooming, (3) groomings--each time the animal lifted one or both front paws and commenced cleaning itself, and (4) boli--the number of fecal boli excreted during the activity period.

The rotarod task provided a measure of motor control (1). The rotarod is a motor-driven, 8-cm-diameter rod, with 25-cm-diameter wafers placed perpendicular to the rod to prevent lateral movement. The rat was placed on the stationary rod oriented with his head in the direction he needed to walk. Timing started when the rod was put into motion. The rod started at 5 rpm and speeded up at a constant acceleration of 1 rpm/sec. When the animal fell (or jumped) from the rod, microswitches were closed to stop the timer and "on rod" time (T) was recorded. Electric grids beneath the rotating rod produced a footshock when the animal jumped to the floor. The shock was set at 0.1 mA and presented for 1 sec.

This task required animal training. The training consisted of placing each animal on the rod a minimum of twice a day for five training days. The training group consisted of 156 rats. The 86 animals with the highest and most consistent run times were divided into the test groups of Table 1. The percentage of trainable animals was consistent with previous reports (1). The average score for the trained animals was between 13 and 17 sec. Animals which did not learn the task obtained scores of 3-4 sec. These animals would stand on the rod until they slid off, a quarter to a third of one revolution. Therefore, the operational range for the rotarod task was from about 4 to 17 sec.

Test Sequence

The radiation exposure facilities were located some 3 km from the behavioral testing laboratory. To insure that the predetermined time sequence was operational, testing started with a "dry run" (Test 1). The dry run was performed the day before the actual exposure day and consisted of sham radiation, placebo injection, transportation, and behavioral testing of all animals. The actual radiation exposure day (Test 2) consisted of radiation exposure (or sham) followed by physostigmine (or placebo) injection, transportation, and the same test battery. Animals were confined in plexiglas tubes and irradiated (or shammed) eight at a time. Each group of eight irradiated animals were divided between test groups 3 and 4. Likewise, sham-irradiated animals were divided between groups 1 and 2. Although all animals were handled in identical fashion during a test day, it should be noted that each test day was unique. Test times 3 and 4, for example, involved no transportation or confinement.

The test sequence for all test groups was as follows:

- a. Each animal weighed (not done before Test 2).
- b. Radiation exposure or sham
 - (1) Test 1--all animals received sham radiation

- (2) Test 2--sham or radiation exposure
- (3) Tests 3 and 4--no sham or radiation exposure
- c. Subcutaneous injection of physostigmine or 0.9% normal saline (placebo), each test time.
- d. Returned to home cage for 30 min and transported during Tests 1 and 2.
- e. Placed in an activity monitor for 2.5 min.
- f. Removed from activity monitor and placed on a rotarod treadmill. All testing was done between 0800 and 1300 in December 1982.

RESULTS

The results of the four test sessions are presented in Table 2 and Figure 1.

Summary of Results:

1. A significant decrease in body weight occurred for both radiation groups. No difference in weight loss was observed between the radiation-only and radiation-plus physostigmine groups (see Table 2, Test 3).
2. An analysis of variance across the test groups indicated a significant effect of ionizing radiation and physostigmine and a significant interaction between the two treatments which was task dependent (see Appendix A).
3. The physostigmine-only group's rotarod performance was consistently 40% below controls: i.e., no repeated exposure effects (Fig. 1).
4. Radiation exposure produced a 30% rotarod performance deficit 45 min postexposure, which was reduced to a 60% deficit by 8-days postexposure. A 60% performance deficit was the maximum observed under the experimental conditions used.
5. The animals which received both ionizing radiation and physostigmine (combined exposure group) were unable to perform the rotarod task above the 60% minimum performance level on any test time, which was consistently lower than any of the other test groups.
6. In addition to weight loss, one animal from the combined exposure group died on day 6 postirradiation and one from the radiation-only group died 30 min after Test 4.

It deserves repeating that each test day was completely independent in terms of handling, previous experience, etc. (see Methods). Therefore, the

TABLE 2. RESULTS OF BEHAVIORAL TESTS OF FOUR TREATMENT GROUPS
TAKEN AT FOUR TEST TIMES (All data listed as mean \pm SEM)

Group number	Treatment	Weight	Rotarod score	Crossings	Activity Rearings	Groomings	Boli excreted
TEST 1							
One-Day Preirradiation (No Radiation or Physostigmine Exposure)							
1	Controls	307 \pm 5	11.8 \pm 1.1	50 \pm 4	11.3 \pm 1.3	1.3 \pm 0.2	0.05 \pm .05
2	Phy only	301 \pm 7	12.2 \pm 1.3	48 \pm 3	10.6 \pm 1.1	0.9 \pm 0.3	0.05 \pm .05
3	Rad only	311 \pm 4	13.2 \pm 1.8	51 \pm 3	12.2 \pm 1.2	1.1 \pm 0.3	0 \pm 0
4	Rad+Phy	305 \pm 6	12.4 \pm 1.3	48 \pm 3	10.3 \pm 1.1	0.7 \pm 0.2	0.05 \pm .05
TEST 2							
45-Min Postirradiation							
1	Controls		15.3 \pm 2.0	27 \pm 4	4.6 \pm 1.0	0.5 \pm 0.2	0.64 \pm .36
2	Phy only		8.9 \pm 1.5*	22 \pm 3	1.6 \pm 0.4*	0.4 \pm 0.3	0.30 \pm .21
3	Rad only		10.6 \pm 1.9*	32 \pm 4	6.5 \pm 1.0	1.0 \pm 0.2	0.27 \pm .15
4	Rad+Phy		6.5 \pm 0.8*	17 \pm 2	1.9 \pm 0.7*	0.5 \pm 0.2	0.32 \pm .19
TEST 3							
4-Days Postirradiation							
1	Controls	323 \pm 6	16.7 \pm 2.7	32 \pm 3	6.3 \pm 0.8	1.9 \pm 0.3	0.14 \pm .15
2	Phy only	325 \pm 5	10.1 \pm 1.6*	36 \pm 3	5.2 \pm 1.0	1.4 \pm 0.3	0.45 \pm .21
3	Rad only	291 \pm 3*	7.9 \pm 1.4*	23 \pm 4	4.5 \pm 0.9	1.1 \pm 0.3	0.55 \pm .33
4	Rad+Phy	282 \pm 6*	7.3 \pm 0.9*	27 \pm 3	4.7 \pm 0.9	1.4 \pm 0.3	0.05 \pm .05
TEST 4							
8-Days Postirradiation							
1	Controls	328 \pm 5	12.2 \pm 1.4	26 \pm 4	6.1 \pm 1.3	1.3 \pm 0.2	0.18 \pm .13
2	Phy only	329 \pm 6	7.6 \pm 1.3*	18 \pm 3	1.9 \pm 0.5*	1.2 \pm 0.3	0.25 \pm .15
3	Rad only	286 \pm 7*	5.1 \pm 0.8*	23 \pm 3	4.4 \pm 0.9	1.7 \pm 0.4	0.23 \pm .19
4	Rad+Phy	283 \pm 10*	5.3 \pm 0.8*	18 \pm 3	2.2 \pm 0.5*	1.4 \pm 0.3	0.41 \pm .26

Controls = Sham radiation and placebo injection

Rad = Ionizing radiation exposure

Phy = Physostigmine exposure

* = Significantly different from sham controls (Group 1)
at $P < 0.05$ (See Table A-2)

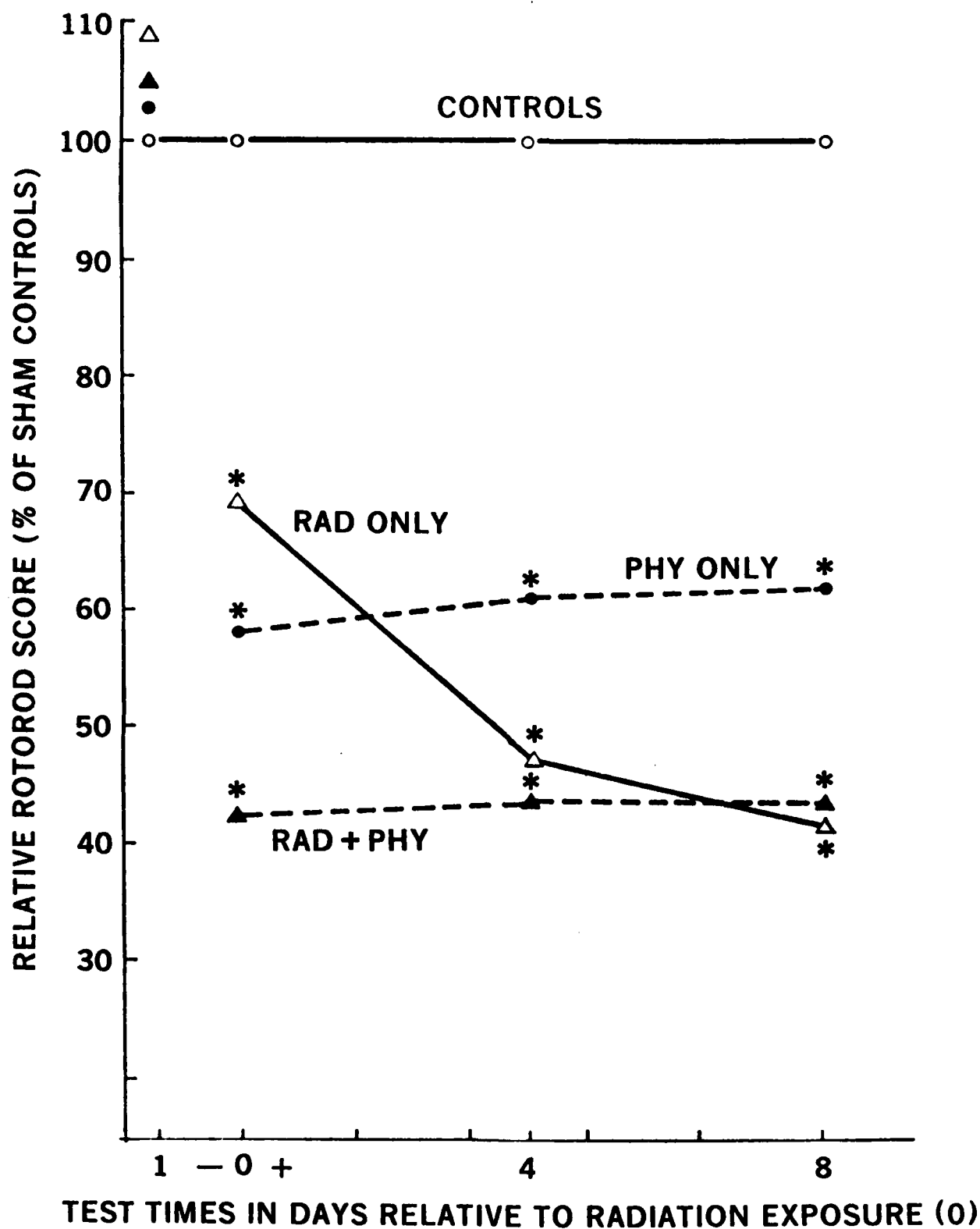


Figure 1. Performance on rotorod task in relation to time of radiation exposure (0). Each test group normalized to its own sham controls.

results of the physostigmine and radiation treatments can only be compared to the sham controls for that test period, as was done for Figure 1. A complete statistical analysis of the data is presented in Appendix A.

DISCUSSION

The objective of this study was to determine if the combined exposure to an anticholinesterase and ionizing radiation would produce a greater performance deficit than either insult presented alone. The study was successful in terms of this primary objective: the combined treatment was more detrimental than either insult presented alone. There was a significant interaction between the two treatments, the extent of which was not clear.

The possible performance range on the rotarod task was too restricted to provide information on the extent of interaction. The deficits due to radiation and physostigmine alone were within the range of the task. However, the combined treatment produced a deficit which was so great that the minimum achievable performance on the task was reached. Some measures on the activity monitor did suggest that the interaction was nonlinear. For example, the number of crossings observed during the second test period suggested a multiple interaction (Table 2). The physostigmine group was 23% below controls, whereas the radiation-only group was 19% above controls. A linear (additive) combination of these data would suggest that the data from the combined treatment group would show a 4% deficit. In fact, a 37% deficit was observed. This nonlinear interaction trend was observed for many of the activity measures (Table 2). Although the statistical analysis indicates a significant nonlinear interaction for the rotarod task (Appendix A, Table A-1, Test 4), this is considered an experimental artifact due to the limited operational range on the task.

For the purpose of defining the extent of interaction more precisely, the performance range on the rotarod task should be extended and the exposure levels reduced. The measures on the activity monitor, while suggestive, were too variable to permit sound conclusions on the extent of interaction.

These data have clearly illustrated an interaction between radiation and anticholinesterase exposure. The mechanism of interaction has yet to be defined. Is the interaction a central nervous system or peripheral phenomenon? Studies designed to determine the extent of interaction and evaluate blood cholinesterase levels could be most useful towards describing the underlying mechanisms.

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APPENDIX A: STATISTICAL ANALYSES OF DATA

The statistical tests included a two-way analysis of variance (ANOVA) and a multiple range test (DUNCAN) for each of four performance measures for each of the test periods. These tests were accomplished using the General Linear Model procedure of the SAS Pack (SAS Institute, Statistical Analysis System, P.O.Box 10066, Raleigh, N.C.). The results of the ANOVA and DUNCAN tests are presented in Tables A-1 and A-2, respectively.

TABLE A-1. ANOVA P Values

Test	Treatment	Body weight	Rotarod task	Activity	
				Crossings	Rearings
Test 1	Phys	0.26	0.88	0.47	0.19
	Rad	0.44	0.58	0.87	0.66
	Rad X Phys	0.93	0.70	0.81	0.71
Test 2	Phys		<0.01	0.01	<0.01
	Rad		0.03	0.85	0.17
	Rad X Phys		0.47	0.19	0.32
Test 3	Phys	0.41	0.05	0.27	0.58
	Rad	<0.01	<0.01	0.01	0.20
	Rad X Phys	0.23	0.11	0.96	0.42
Test 4	Phys	0.90	0.07	0.03	<0.01
	Rad	<0.01	<0.01	0.67	0.43
	Rad X Phys	0.78	0.02	0.73	0.24



TABLE A-2. MULTIPLE RANGE TEST (DUNCAN)

Multiple range test for comparing group means within each 2 X 2 test matrix (Table 1). For each test period and performance measure, treatment groups with the same letters are not significantly different. Groups with dissimilar letters are significantly different ($P < 0.05$). Comparisons across test times and performance measures are not valid.

Group number	Treatment	Weight	Rotarod task	Crossings	Rearings
TEST 1					
1	Control	A	A	A	A
2	Phy only	A	A	A	A
3	Rad only	A	A	A	A
4	Rad + Phy	A	A	A	A
TEST 2					
1	Control		A	AB	A
2	Phy only		B	AB	B
3	Rad only		B	A	A
4	Rad + Phy		B	B	B
TEST 3					
1	Control	A	A	AB	A
2	Phy only	A	B	A	A
3	Rad only	B	B	B	A
4	Rad + Phy	B	B	AB	A
TEST 4					
1	Control	A	A	A	A
2	Phy only	A	B	A	B
3	Rad only	B	B	A	AB
4	Rad + Phy	B	B	A	B

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